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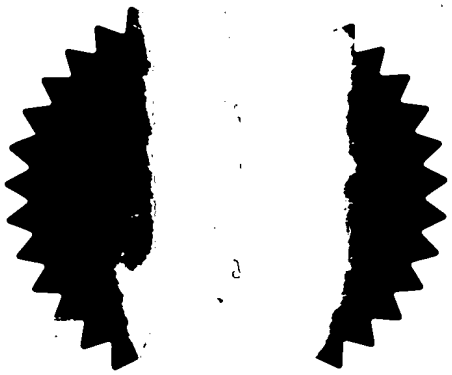

Signed A M Brewer.

Dated 7 November 2001

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Patents Act 7
(Rule)

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24OCT00 E578205-1 C44637
P01/7700 0.00-0025957.2

Request for grant of a patent

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Cardiff Road
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1. Your reference
RC7

2. Patent application number
(The Patent Office will fill in this part) **0025957.2** 24 OCT 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
ALEXANDER ROBERT POWELL
82 BELMONT ST.
SOUTHPORT
MERSEYSIDE
PR8 1SH

Patents ADP number *(if you know it)*
12660060

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention
CELL CULTURE APPARATUS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
82 BELMONT ST
SOUTHPORT
MERSEYSIDE
PR8 1SH

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

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Description	3 + 3
Claim(s)	0
Abstract	0
Drawing(s)	2 + 2

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature A L Rowell Date 22/10/00

12. Name and daytime telephone number of person to contact in the United Kingdom [redacted] 01704 531722

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Cell Culture Apparatus

Technical Field

This invention relates to cell culture apparatus for growing animal cells in rotating cylinders, or roller bottles.

Background

There are a variety of existing types of apparatus in which cells are cultured whilst attached to the interior of horizontally mounted cylinders or bottles which are slowly rotated to ensure that all the cells are regularly bathed in culture media.

In order to increase the productivity of the apparatus, a plurality of bottles or cylinders may be connected together via a common fluid supply/extraction manifold thus allowing fluid to be transferred into or out of a number of vessels simultaneously.

It is essential in such a system to ensure that each vessel is provided with an equal volume of fluid during processing operations. In some systems, for example, US 3,847,749, or EU 0775196, equal fluid distribution is accomplished by means of a multi-channel peristaltic pump, with each vessel being assigned one channel of the pump. Such systems allow the bottles to processed in situ and in the horizontal position.

In other systems, for example US 3,827,943, or US 3,732,149 a drum or rotor housing a plurality of interconnected cylindrical vessels is tilted into the vertical position during fluid transfer operations, thus allowing the fluid level in each vessel to equalise by gravity. This has the advantage of simplicity over systems that require a separate pumping channel for each vessel. Unfortunately, the existing arrangements of tilting rotor devices require air and fluid connections to be provided at opposite ends of the vessels, and cannot therefore utilise conventional roller bottles which are readily available, sterile irradiated, in standardised sizes. It would be advantageous if this type of apparatus could be adapted to utilise standard roller bottles.

Disclosure of Invention

Accordingly, a roller bottle cap is herein provided that allows tilting rotor apparatus such as those disclosed in US 3,827,943, or US 3,732,149 to utilise conventional roller bottles.

A roller bottle cap, adapted to allow fluid transfer into or out of a roller bottle whilst said bottle is inverted vertically, comprising a fluid supply/drain connection arranged at the lowest point of the cap when said bottle is vertically inverted, with venting of the gas space above the fluid during fluid transfer being provided by means of a snorkel tube extending upwards through the fluid, said snorkel tube being arranged substantially along the

central axis of the bottle and provided with micro-porous venting means to atmosphere.

The invention will now be described by way of example, with reference to the following drawings, in which:

Figure 1. Shows a bottle cap fitted to a roller bottle, with the bottle in the vertically inverted position, as would be the case during fluid transfer into or out of the bottle.

Figure 2. Shows an assembly of bottles and caps with interconnecting manifold and a sealable external connection.

Referring to Figure 1, a roller bottle, 1 is provided with a screw fitting cap body 2. The end cover of the cap 2, is formed internally as a shallow inverted cone with a drain connection 6 provided at the apex, or lowest point, such that fluid 5 may be completely drained from the bottle whilst it is vertically inverted as shown. Fluid supply to, or extraction from, the bottle 1, is facilitated via a fluid supply/extraction manifold 7, communicating with the drain connection 6. During fluid transfer operations into or out of the bottle 1, venting of the gas space above the fluid 5 is facilitated by means of a snorkel tube 4, substantially on the central axis of the bottle 1, and passing upwards through the fluid 5. The snorkel tube 4 is fitted with micro-porous filtering means 3 to prevent air–born contamination entering the vessel. The snorkel tube 4 may be provided with graduations, as shown, to indicate the fluid volume contained within the bottle. The inner end of the snorkel tube 4 may be further provided with a fluid trap 11 to prevent fluid splashes from entering the snorkel tube 4, during handling of the bottle.

During cell incubation stages, the roller bottle is turned to the horizontal position and rotated slowly, in the normal manner.

Referring now to figure 2, a plurality of caps 2 and bottles 1 may be connected together via a common fluid supply/extraction manifold 7, and the manifold 7 provided with a sealable external connection 8. The bottles 1 are arranged with their central axis parallel, and may be secured together into a stack or assembly, by for example binding straps 12.

During fluid transfer operations, the stack of bottles is vertically inverted, as shown in figure 2. Equal distribution of fluid to all bottles is then assured by equalisation of the fluid 5 level via the manifold 7 under the effect of gravity. As an alternative to volume graduations on the snorkel tube as described above, the bottles 1 may be provided with externally printed graduations 9, showing the fluid volume contained therein when the bottle is inverted.

During cell incubation stages, the bottle stack or assembly, is turned to the horizontal position and may be located within a drum, or rotor and rotated bodily about a horizontal axis in the known manner. In these circumstances, clamps or valves 10 may be provided to prevent siphoning of fluid between bottles whilst the stack or bottle assembly is being tilted between the vertical and horizontal positions.

It may be convenient to provide a sterile disposable assembly comprising a plurality of interconnected caps, a manifold and a sealable external connection. Roller bottles can then be fitted to the cap/manifold assembly, prior to use.

It may further be convenient to provide a sterile disposable assembly comprising a plurality of interconnected caps, a manifold, and a sealable external connection, with the roller bottles already fitted. This provides an advantage to the user in that it eliminates the need to assemble the caps, manifold and bottles under sterile conditions prior to using the system, and thus substantially reduces the risk of contamination during the set up procedure.

Where a plurality of caps and bottles are connected together, it may be convenient to provide a single micro-porous vent filter to atmosphere, communicating with each bottle cap snorkel tube 4 via a multi-way vent manifold, (not shown), rather than providing a separate vent filter for each bottle cap.

FIGURE 1

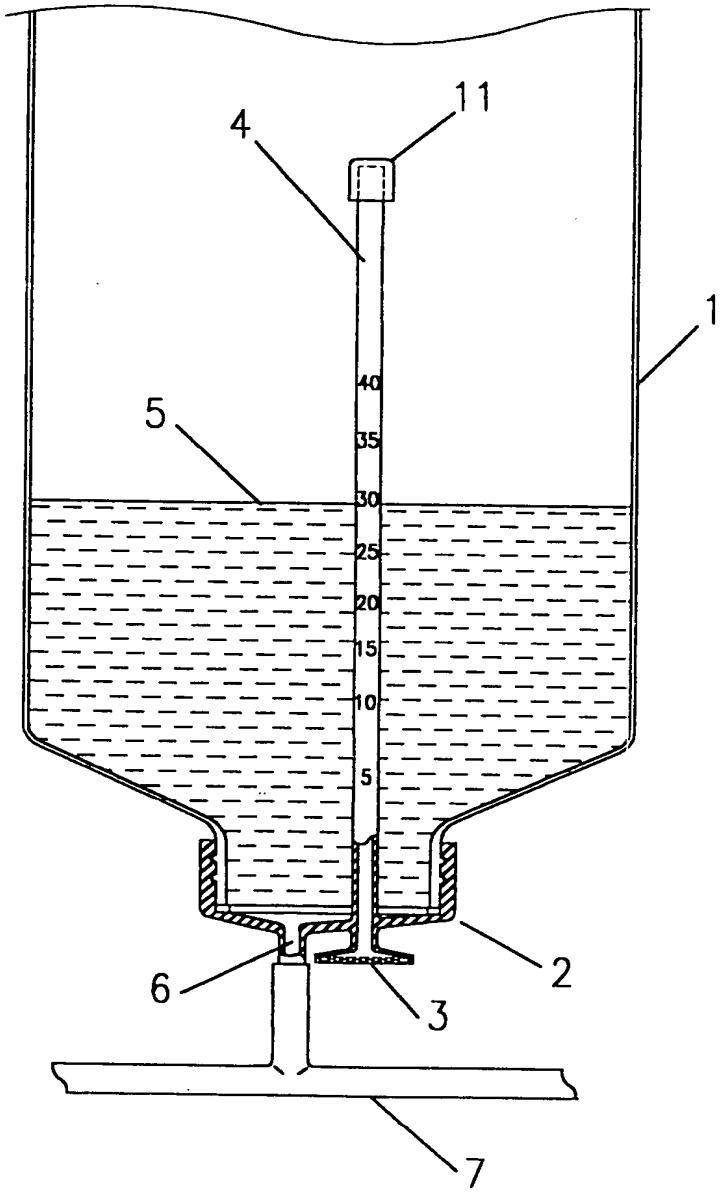
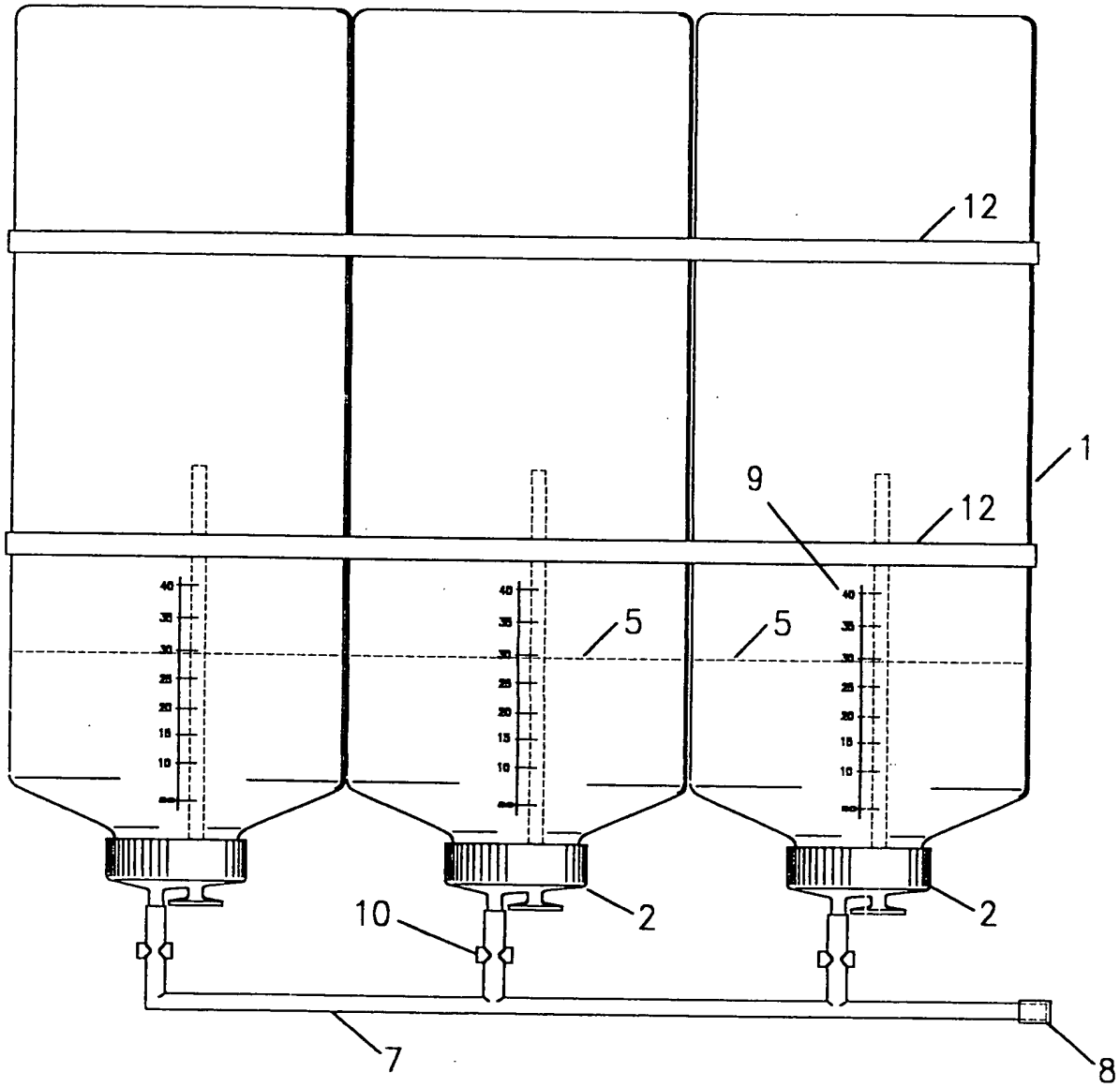


FIGURE 2



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Signed A W Brewer.

Dated 8 November 2001

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1. Your reference

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2. Patent application number
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P01/7700 0.00-0026661.9

0026661.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ALEXANDER ROBERT POWELL
82 BELMONT ST
SOUTHPORT
MERSEYSIDE
PR8 1JH

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CELL CULTURE APPARATUS

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See note (d))

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Signature A R Powell Date 31/10/00

12. Name and daytime telephone number of person to contact in the United Kingdom 01704 531 722

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Background

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In order to increase the productivity of the apparatus, a plurality of bottles or cylinders may be connected together via a common fluid supply/extraction manifold thus allowing fluid to be transferred into or out of a number of vessels simultaneously.

It is essential in such a system to ensure that each vessel is provided with an equal volume of fluid during processing operations. In some systems, for example, US 3,847,749, or EU 0775196, equal fluid distribution is accomplished by means of a multi-channel peristaltic pump, with each vessel being assigned one channel of the pump. Such systems allow the bottles to processed in situ and in the horizontal position.

In other systems, for example US 3,827,943, or US 3,732,149 a drum or rotor housing a plurality of interconnected cylindrical vessels is tilted into the vertical position during fluid transfer operations; thus allowing the fluid level in each vessel to equalise by gravity. This has the advantage of simplicity over systems that require a separate pumping channel for each vessel. Unfortunately, the existing arrangements of tilting rotor devices require air and fluid connections to be provided at opposite ends of the vessels, and cannot therefore utilise conventional roller bottles which are readily available, sterile irradiated, in standardised sizes. It would be advantageous if this type of apparatus could be adapted to utilise standard roller bottles.

Disclosure of Invention

According to the present invention there is provided, cell culture apparatus comprising a rotor, releasably housing a plurality of cell culture vessels / roller bottles, with means provided to allow rotation of the rotor at a controlled speed about a substantially horizontal axis for cell incubation purposes, with further means provided to allow the rotational axis of the said rotor and bottles housed therein to be tilted to the vertical position such that the cap end of the bottles is downward, each bottle being provided with a cap equipped with a fluid supply / drain connection arranged at the lowest point of the cap when said bottle is vertically inverted with the cap downwards, a manifold with one or more sealable external connections and a plurality of connections communicating with the fluid supply / drain connection of each bottle cap, with venting of the gas space within the bottle during fluid transfer being provided by means of a snorkel tube passing upwards through the fluid and formed as an internal extension of the bottle cap, said snorkel tube extending into the

body of the bottle and arranged substantially along the central longitudinal axis of the bottle, the said snorkel tube being further provided with micro-porous venting means to atmosphere, the arrangement of the parts being such that fluid transfer into or out of the bottles is accomplished via the said manifold external connection whilst the rotor and bottles are in the vertically inverted position.

The invention will now be described by way of example with reference to the following drawings, in which:

Figure 1. Shows a cell culture vessel / roller bottle in the vertically inverted position, as would be the case during fluid transfer into or out of the bottle.
Figure 2. Shows an assembly of bottles and caps with interconnecting manifold and a sealable external connection.
Figure 3. Shows a front view of an apparatus with the rotor in the horizontal cell incubation position, said apparatus being adapted to allow individual bottles to be removed for inspection during cell culture stages.
Figure 4. shows a side view of the apparatus with the rotor in the horizontal cell incubation position.
Figure 5. shows a front view of the apparatus with the rotor in the vertical position to allow fluid transfer into or out of the bottles.

Referring to Figure 1, a cell culture vessel / roller bottle, 1 is provided with a screw fitting cap 2. The end cover of the cap 2, is formed internally as an inverted cone with a drain connection 6 provided at the apex, or lowest point, such that fluid 5 may be completely drained from the bottle whilst it is vertically inverted as shown. Fluid supply to, or extraction from, the bottle 1, is facilitated via a fluid supply/extraction manifold 7, communicating with the drain connection 6.

During fluid transfer operations into or out of the bottle 1, venting of the gas space above the fluid 5 is facilitated by means of a snorkel tube 4, substantially on the central axis of the bottle 1, and passing upwards through the fluid 5. The snorkel tube 4 is fitted with micro-porous filtering means 3 to prevent air–born contamination entering the vessel. The snorkel tube 4 may be provided with graduations, as shown, to indicate the fluid volume contained within the bottle. The inner end of the snorkel tube 4 may be further provided with a fluid trap 11 to prevent fluid splashes from entering the snorkel tube 4, during handling of the bottle. Alternatively, the micro-porous filter 3 may comprise a hydrophobic membrane located at the inner end of the snorkel tube 4, such that gas or air can pass into or out of the vessel whilst preventing liquid entering the dip tube 4.

During cell incubation stages, the roller bottle is turned to the horizontal position and rotated slowly, in the normal manner.

Referring now to figure 2, a plurality of caps 2 and bottles 1 may be connected together via a common fluid supply/extraction manifold 7, and the manifold 7 provided with a sealable external connection 8. The bottles 1 are arranged with their central axis parallel, and may be secured together into a stack or assembly, by for example binding straps 12.

During fluid transfer operations, the stack of bottles is vertically inverted, as shown in figure 2. Equal distribution of fluid to all bottles is then assured by equalisation of the fluid 5 level via the manifold 7 under the effect of gravity. As an alternative to volume graduations on the snorkel tube as described above, the bottles 1 may be provided with externally printed graduations 9, showing the fluid volume contained therein when the bottle is inverted.

During cell incubation stages, the bottle stack or assembly, is turned to the horizontal position and may be located within a drum, or rotor and rotated bodily about a horizontal axis in the known manner. In these circumstances, clamps or valves 10 may be provided to prevent siphoning of fluid between bottles whilst the stack or bottle assembly is being tilted between the vertical and horizontal positions.

It may be convenient to provide a sterile disposable assembly comprising a plurality of interconnected caps, a manifold and a sealable external connection. Roller bottles can then be fitted to the cap/manifold assembly, prior to use.

It may further be convenient to provide a sterile disposable assembly comprising a plurality of interconnected caps, a manifold, and a sealable external connection, with the roller bottles already fitted. This provides an advantage in that it eliminates the need to assemble the caps, manifold and bottles under sterile conditions prior to using the system, and thus substantially reduces the risk of contamination during the set up procedure.

Where a plurality of caps and bottles are connected together, it may be convenient to provide a single micro-porous vent filter to atmosphere, (not shown) communicating with each bottle cap snorkel tube 4 via a multi-way vent manifold, (not shown), rather than providing a separate vent filter for each bottle cap.

Referring now to figures 3 and 4, an embodiment of the invention is shown which is adapted to allow the bottles 1 to be removed individually for inspection during cell incubation stages. The apparatus is shown with the rotor in the horizontal cell incubation position.

A plurality of bottles 1 are housed within a rotor 13, and releasably secured by means of retaining catches 14. In order to prevent rotation of the bottles 1 relative to the rotor 13, the catch 14 may be arranged so as to engage with one or more indentations (not shown) in the shoulder of the bottle 1. A manifold 7, equipped with a sealable external connection 8 is releasably secured to the rotor 13, and communicates with the supply / drain connection of each bottle 1 by means of flexible interconnecting tubes 20. The length of each tube 20 is sufficient to allow the bottles 1 to be removed from the rotor 13, the excess length of the tubing being stored the rest of the time by being wound around the caps 15 in the manner previously revealed in EU 0775,196.

During cell incubation stages, the rotor 13 is rotated about the horizontal axis at a controlled speed by motor-gear unit 19 and a speed controller (not shown).

The rotor 13 is mounted upon a tilting frame 16, that may be rotated about pivot bearings 18, which are mounted upon a supporting frame 17. The tilting frame 16 may be locked in the vertical or horizontal position by locking means not shown. The interconnections 20 between each bottle 1 and the manifold 7 may be provided with valves 10, to prevent fluid siphoning between the bottles 1 when the tilting frame 16 and rotor 13 are in intermediate positions between vertical and horizontal.

Referring now to figure 5, a front view of the apparatus is shown, with the rotor 13 and tilting frame 16 in the vertical position to facilitate fluid transfer into or out of the bottles 1. Fluid is transferred by means of an umbilical 21, that is connected aseptically to the sealable external connection 8 (figures 3 & 4), and by pumping means (not shown), or by gravity head from a receiver (not shown).

As fluid is transferred into or out of the bottles 1, the gas space above the fluid 5 is vented to atmosphere via the snorkel tubes 4. Equal distribution of fluid 5 between bottles 1 is assured by allowing the levels to equalise under gravity and by equalisation of the pressure within the gas space above the fluid 5 by snorkel tubes 4.

FIGURE 1

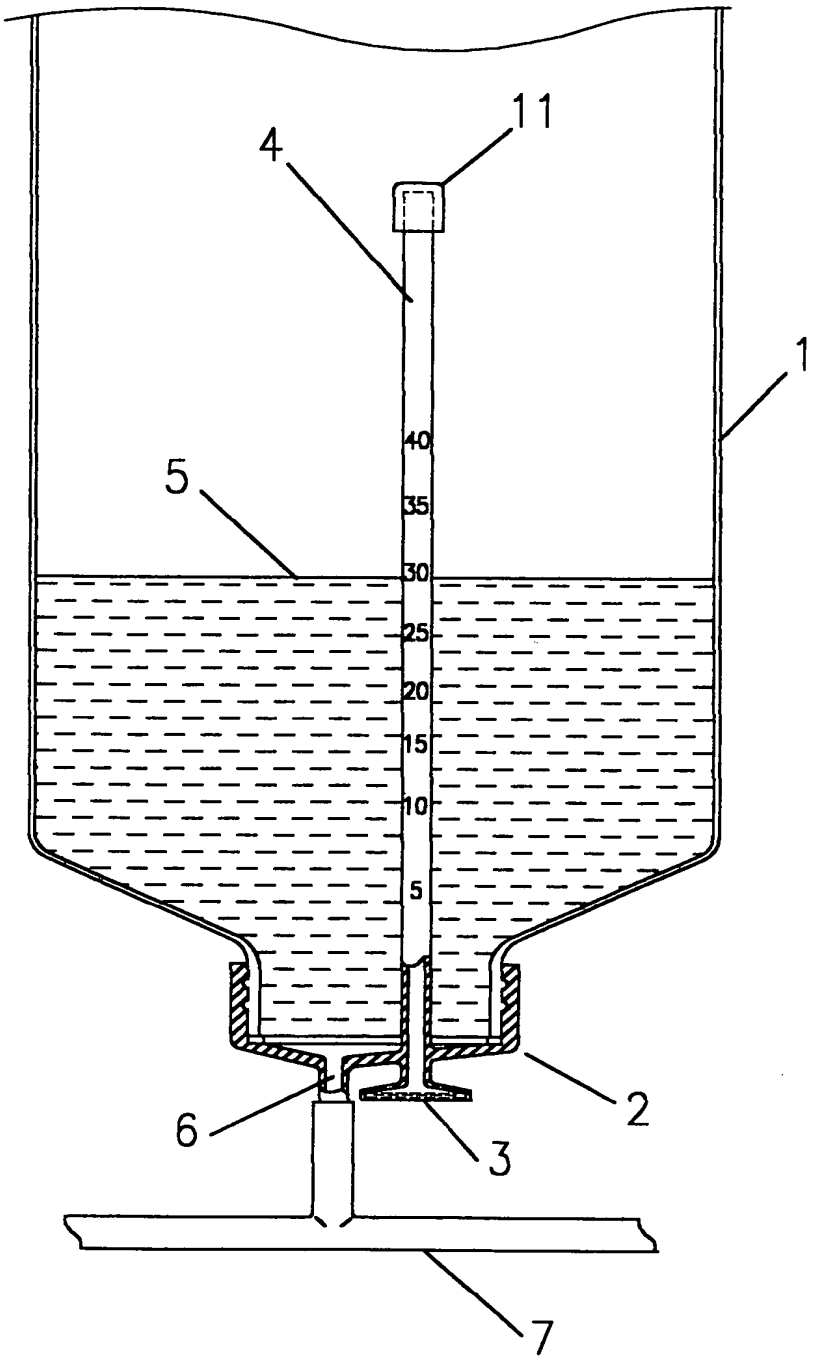

FIGURE 2

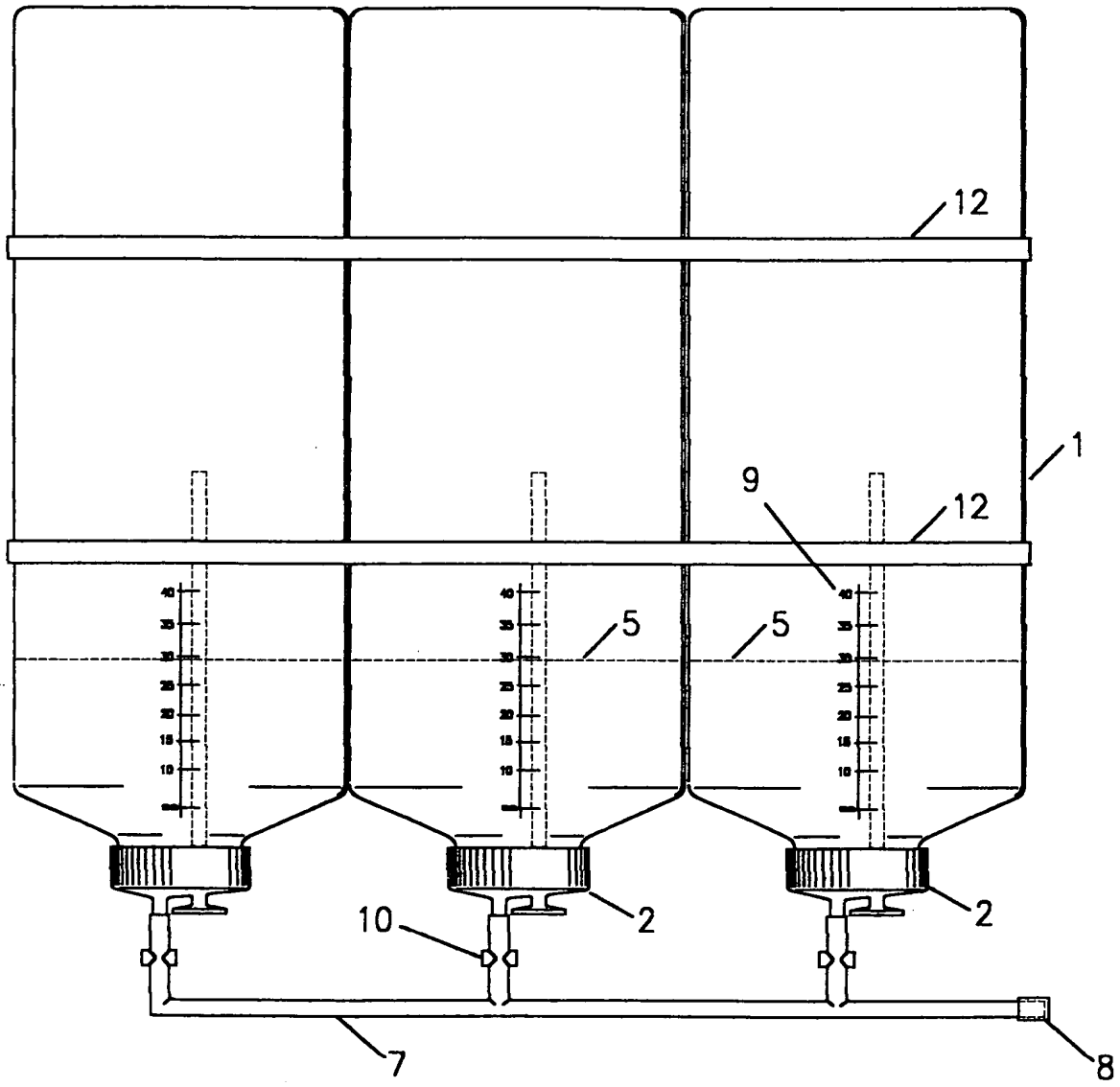

FIGURE 3

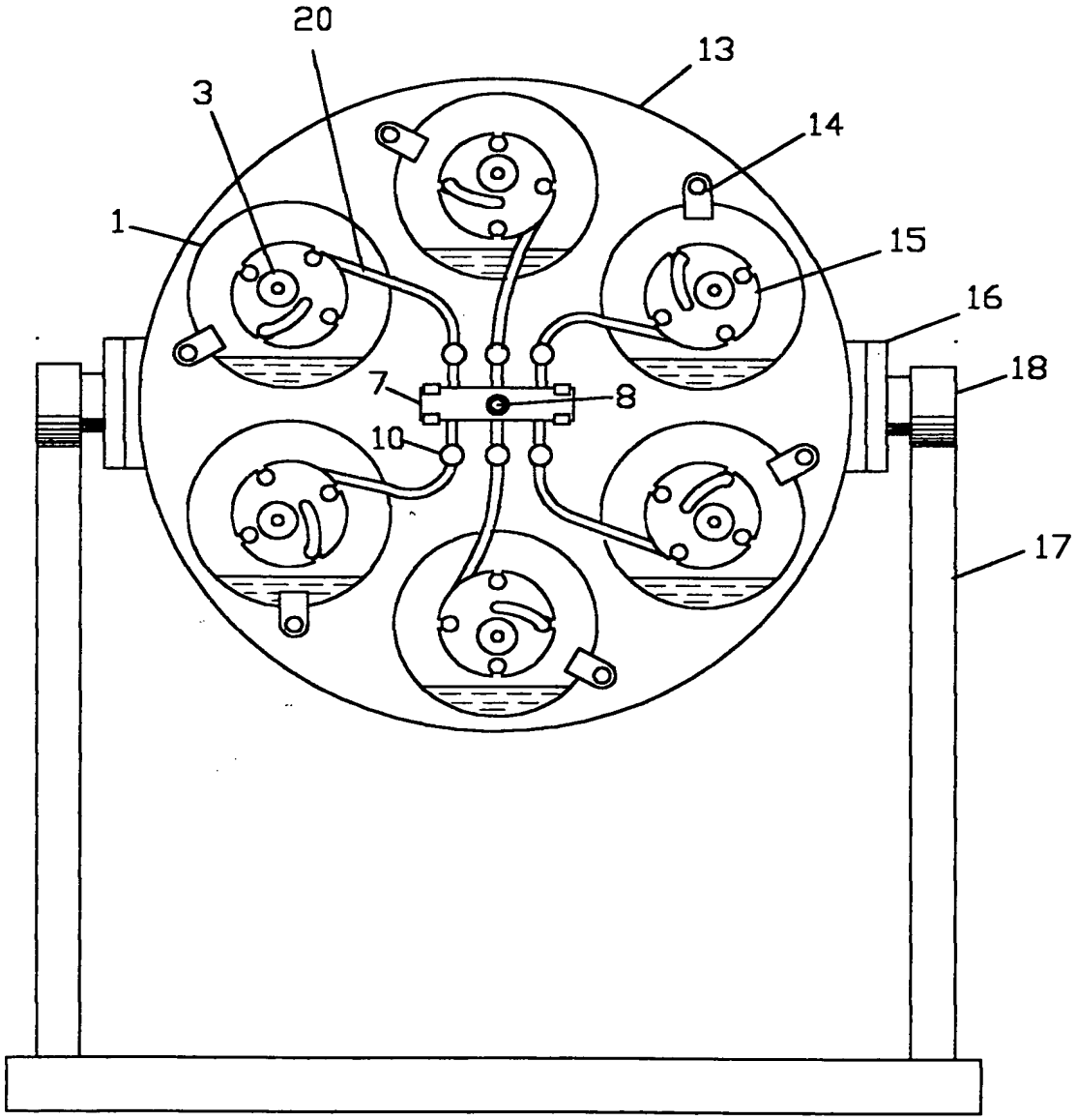

FIGURE 4

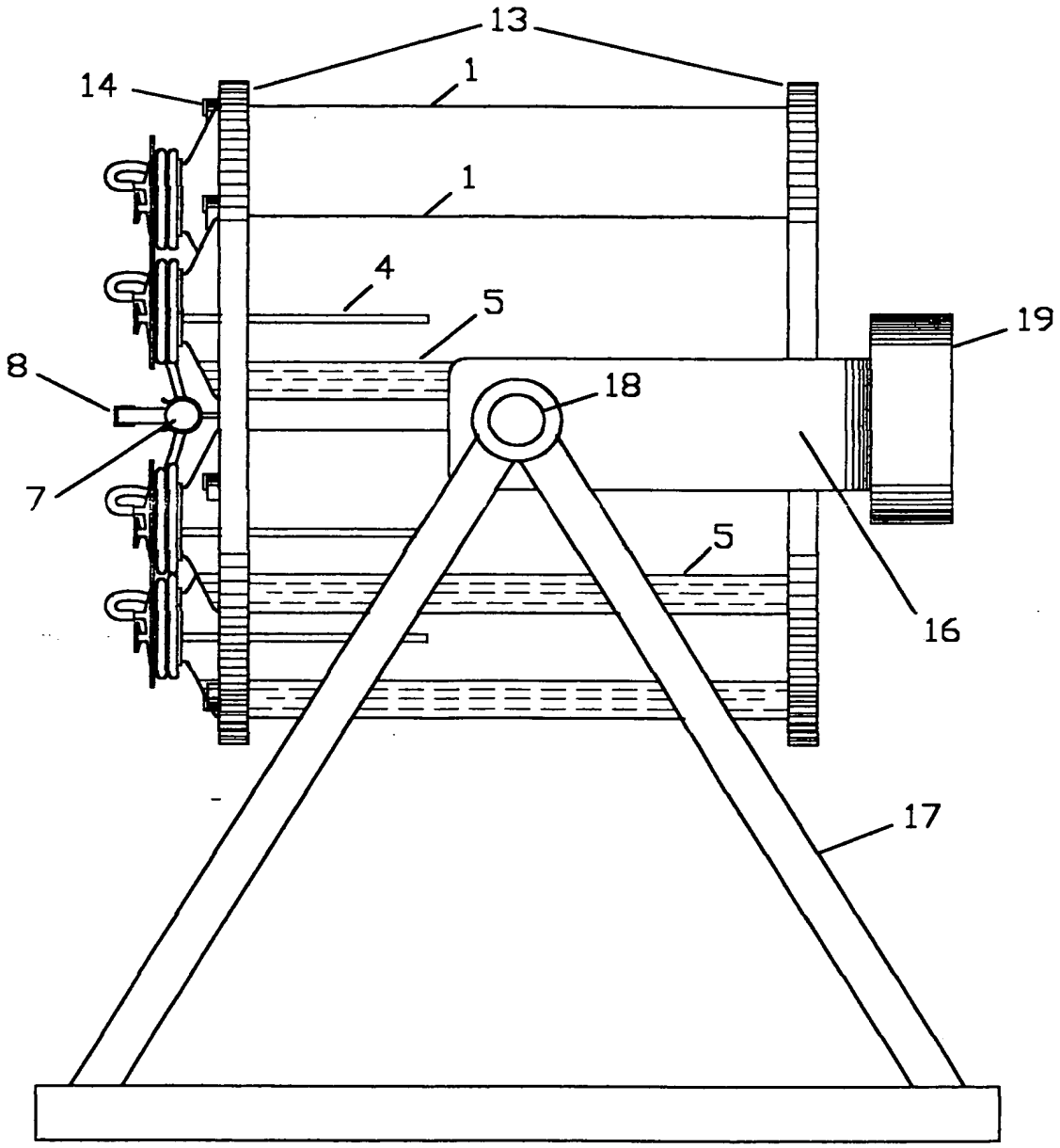

FIGURE 5